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תכשירי רוקחות המכילים (+)-קנאבידיול ותולדות שלו, ומספר תולדות חדשות שכולו

(English)

(באנגלית)

PHARMACEUTICAL COMPOSITIONS CONTAINING (+) CANNABIDIOL AND DERIVATIVES  
THEREOF AND SOME SUCH NOVEL DERIVATIVES

hereby apply for a patent to be granted to me in respect thereof.

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תכשירי רוקחות המכילים (+)-קנאבידיול ותולדות שלו, ומספר תולדות חדשות שבאלו

**PHARMACEUTICAL COMPOSITIONS CONTAINING (+) CANNABIDIOL AND DERIVATIVES  
THEREOF AND SOME SUCH NOVEL DERIVATIVES**

### **Field of the Invention**

The invention relates to use of (+)-cannabidiol derivatives as activators of the peripheral cannabinoid system and to some such novel (+)-cannabidiol derivatives. The (+)-cannabidiol derivatives of the invention do not activate the central nervous system, particularly the brain, are thus devoid of psychoactive side effects and are particularly useful as modulators/regulators of the immune system and the gastrointestinal tract.

### **Background of the Invention**

Throughout this application various publications are referred to in square brackets. A full list of these references appears at the end of the description, immediately preceding the claims. These publications, including references referred to therein, are fully incorporated herein by reference.

Delta-9 tetrahydrocannabinol ( $\Delta^9$ -THC) and (-)-cannabidiol (CBD) are the two major constituents of the *Cannabis sativa* (marihuana) plant.  $\Delta^9$ -THC is psychoactive and binds to cannabinoid CB<sub>1</sub> receptors located in brain and the periphery [Herkenham, 1995; Pertwee, 1997], as well as to CB<sub>2</sub> receptors which are located exclusively on nonneural tissue, such as immune cells [Pertwee, 1997]. CBD binds neither receptor and is not psychoactive.  $\Delta^9$ -THC is considered to be responsible for virtually all central effects observed with the cannabis plant (marihuana) and for many of its peripheral effects [Pertwee, 1997; Mechoulam et al., 1998; Fride and Sanudo-Pena, 2002]. Peripheral effects include inhibition of gastrointestinal activity [Pinto et al. 2002] and anti-inflammatory effects [Mechoulam et al., 1998].

In view of the abundance of CB<sub>1</sub> and CB<sub>2</sub> receptors on immune cells [Galiegue et al., 1995; Pertwee, 1997], it is not surprising that cannabinoids are effective regulators of the inflammatory process

including peripheral pain [Hanus et al., 1999; Mechoulam et al., 1998; Malfait et al., 2000].

There is ample evidence *in vitro* and *in vivo* for an inhibitory action of  $\Delta^9$ -THC and other cannabinoids and endocannabinoids (anandamide, 2-arachidonoyl glycerol, 2-AG and noladine ether, see Fride, 2002) on intestinal motility in various species such as mice, rats and guinea pigs [Pertwee 2001; Pinto et al., 2002]. Early work includes *in vivo* evidence for an inhibitory effect of  $\Delta^9$ -THC on intestinal motility in mice [Chesher et al., 1973]. Endocannabinoid-induced inhibition of intestinal motility was first demonstrated for anandamide as a near cessation of defecation in mice [Fride and Mechoulam, 1993; Fride, 1995].

Most evidence suggest that the cannabinoid-induced gastrointestinal inhibition is mediated by CB<sub>1</sub> receptors [Colombo et al., 1998 ; Pertwee 2001; Pinto et al., 2002; Calignano et al., 1997]. This is in agreement with a presence of CB<sub>1</sub> receptors and CB<sub>1</sub> receptor mRNA [Casu et al., 2003; Griffin et al., 1997], but not of CB<sub>2</sub> receptor mRNA in the mysenteric plexus of the gut. It has also been determined that gastrointestinal transit is regulated locally in the periphery rather than by centrally located CB<sub>1</sub> receptors [Izzo et al., 2000; Landi et al., 2002].

On the other hand, the inventors have shown previously that the selective CB<sub>2</sub> receptor agonist, HU-308, inhibited defecation which was antagonized by the selective CB<sub>2</sub> receptor antagonist SR144528, but not by the CB<sub>1</sub> receptor antagonist SR141716A [Hanus et al., 1999].

These findings suggest that cannabinoids may be developed as therapeutic agents in conditions such as inflammatory pain and inflammatory bowel diseases. The significant drawback for the use of cannabis or  $\Delta^9$ -THC is the unwanted psychoactive side effects, such as anxiety, confusion and

memory impairment, which may be observed with higher doses [Robson, 2001]. Therefore current efforts are aimed at developing cannabinoids with medical benefits but which are devoid of psychoactive side effects.

Despite the dichotomy between  $\Delta^9$ -THC and CBD, CBD displays a number of pharmacological activities, which are similar to those of  $\Delta^9$ -THC. These include antiemetic [Parker et al., 2002] and antiinflammatory effects [Malfait et al., 2000]. Being devoid of psychoactive effects, CBD is a good candidate for future development of peripherally acting cannabinoid-like drugs.

The present inventors have previously described several (-)-CBD derivatives and their activity as antiinflammatory agents, analgesics, neuroprotective and antipsychotic as well as anti-cancer agents [WO01/95899].

In a previous report, [Bisogno et al., 2001] the inventors described the biochemical properties of a number of derivatives of the natural (-)-CBD as well as the synthetic (+)-CBD, namely (+)-CBD-DMH and (+)-7-OH-CBD-DMH. Only the latter (+) analogues were found to bind CB<sub>1</sub> and/or CB<sub>2</sub> receptors. Vannilloid VR1 receptors or increased levels of the endocannabinoid anandamide may mediate effects of some, but not all analogues. Based on such findings, candidates for anti-inflammatory or other therapeutic activity may be developed.

In search for selective agonists/antagonists of the peripheral cannabinoid system, which would not affect the central nervous system, which are an object of the present invention, the inventors examined the aforementioned (+)-CBD, (+)-CBD-DMH and (+)-7-OH-CBD-DMH, and several novel (+)CBD analogues, particularly (+)-7-OH-CBD, (+)-COOH-CBD and (+)-COOH-CBD-DMH, for central as well as peripheral activity

in mice. Some synthetic (+)-CBD derivatives were indeed found to possess such selective activity.

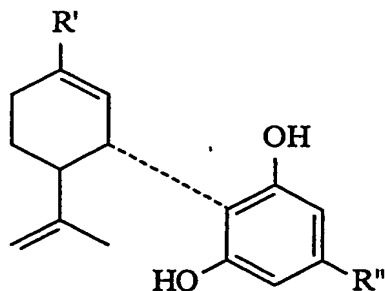
It is therefore an object of the present invention to provide (+)-CBD derivatives for use as selective modulators of the peripheral nervous system. Further objects of the present invention are to provide (+)-CBD derivatives for use as analgesics, anti-inflammatories and anti-diarrheal agents.

It is a further object of the present invention to provide novel (+)-CBD derivatives, which may be useful as selective modulators of the peripheral nervous system.

These and other objects of the invention will become apparent as the description proceeds.

#### Summary of the Invention

The present invention relates to an optically pure (+) enantiomer of a compound of the formula:



Formula I

wherein R' designates a —COOH or —CH<sub>2</sub>OH group and R'' designates a straight or branched C<sub>5</sub>-C<sub>12</sub> alkyl group, an —OR''' group wherein R'''

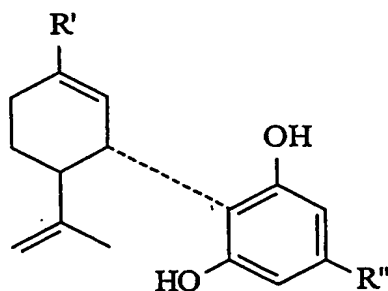
designates a straight or branched C<sub>5</sub>-C<sub>9</sub> alkyl group which may be optionally substituted with a phenyl group on the terminal carbon atom, or a  $-(CH_2)_n-O-C_{1-5}$  alkyl group, wherein n is an integer of from 1 to 7, with the proviso that R' is not  $-CH_2OH$  when R''' is dimethylheptyl, and pharmaceutically acceptable salts and esters thereof.

In preferred compounds, R' is  $-COOH$  and R''' is a pentyl or dimethylheptyl group.

In other preferred compounds, R' is  $-CH_2OH$  and R''' is a pentyl group.

The invention also relates to a pharmaceutical composition containing as active ingredient a compound of formula I wherein the substituents are as defined as above, and optionally further comprising at least one pharmaceutically acceptable carrier, additive, excipient or diluent. The pharmaceutical composition of the invention may optionally further comprise an additional pharmaceutically active agent.

In a further aspect the invention relates to use of a (+) enantiomer of a compound of the formula:



Formula Ia

wherein R' designates a CH<sub>3</sub>,  $-COOH$  or  $-CH_2OH$  group and R'' designates a straight or branched C<sub>5</sub>-C<sub>12</sub> alkyl group, an  $-OR'''$  group



wherein R''' designates a straight or branched C<sub>5</sub>-C<sub>9</sub> alkyl group which may be optionally substituted with a phenyl group on the terminal carbon atom, or a  $-(CH_2)_n-O-C_{1-5}$  alkyl group, wherein n is an integer of from 1 to 7, or a pharmaceutically acceptable salt or ester as a selective modulator of the peripheral cannabinoid system.

Preferably, the (+) enantiomer of a compound of formula Ia is used as an analgesic agent, a modulator of the immune system, an antiinflammatory agent, or as a modulator of the gastrointestinal tract, particularly an anti-diarrheal agent.

The invention further relates to the use of a (+) enantiomer of a compound of the formula (Ia) wherein the substituents are as defined above or a pharmaceutically acceptable salt or ester thereof, in the preparation of a pharmaceutical composition for the selective treatment of disorders associated with the peripheral cannabinoid system.

In particular embodiments, the pharmaceutical compositions prepared in accordance with the invention are an analgesic pharmaceutical compositions, pharmaceutical compositions for the treatment of immune disorders associated with the peripheral cannabinoid system, antiinflammatory compositions, and pharmaceutical compositions for the treatment of a disorder associated with the gastrointestinal tract, particularly an anti-diarrheal pharmaceutical compositions.

The invention further relates to methods of treatment of disorders associated with the peripheral cannabinoid system by administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula Ia or of a pharmaceutical composition in accordance with the invention.

The invention will be described in more detail on hand of the following figures.

### Brief Description of the Figures

#### Figure 1: Lack of effects of (+)-CBD

(+)-CBD was injected (20 mg/kg) *i.p.* into female Sabra mice. Sixty min later, the animals were tested for central (ambulation and rearing in an open field, immobility on a ring, hot plate analgesia and hypothermia) and peripheral (intestinal motility) effects.

#### Figure 2: Central cannabinoid effects

(+)-7-OH-CBD, (+)-7-OH-CBD-DMH, (+)-COOH-CBD, (+)-COOH-CBD-DMH and (+)-CBD-DMH (20 mg/kg) were injected *i.p.* into female Sabra mice. Mice were tested 60 min later for centrally mediated effects (ambulation and rearing in an open field, catalepsy (immobility) on an elevated ring and hypothermia. (+)7OH-CBD-DMH was very potent whereas none of the other (+)CBD derivatives had any effect.

\*\*\*)  $P < 0.001$  cf. Vehicle-injected mice.

#### Figure 3: Lack of central effects of (+)-CBD-DMH using THC as a reference drug

Both drugs were injected *i.p.* at a dose of 20 mg/kg (see Legend of Fig 2 for full explanations). \*)  $P < 0.05$  cf Vehicle; \*\*\* )  $P < 0.001$  cf Vehicle.

#### Figure 4: Inhibition of Intestinal Motility

Sixty min after *i.p.* injections of (+)-CBD-DMH or (+)-7-OH-CBD-DMH, defecation (intestinal motility) was completely blocked.

\*\*\*) different from vehicle control ( $P < 0.001$ ).

#### Figure 5: Lack of centrally mediated analgesia on hot plate

By (+)CBD-DMH (20 mg/kg) (A) and (+)OH-CBD-DMH (B) (20 mg/kg).

\*\*\*)  $P < 0.001$  vs control (vehicle)

Figure 6: Analgesic effect of (+)-CBD-DMH in a model of non-centrally mediated pain

Formalin (4%) was injected in the left hind footpad and the number of licks of the injected foot were recorded for each 5 min interval for the 60 min starting immediately after formalin application. (+)-CBD-DMH almost completely prevented the second phase of pain.

Figure 7: Antiinflammatory effect in a model of arachidonic acid-induced ear inflammation in the mouse

Antiinflammatory effect of (A) 40 (B) 10 mg/kg (+)-CBD-DMH compared to Indomethacin (20mg/kg) or (C) 40 mg/kg of (+)-CBD or (+)-7-OHCBDDMH in a model of arachidonic-acid-induced ear inflammation in the mouse: Equal potencies of (+)CBD-DMH and Indomethacin.

\*)  $P < 0.05$  different from vehicle, or (if adjacent to vehicle-data) different from both test drugs

\*\*\*)  $P < 0.001$  different from vehicle, or (if adjacent to vehicle-data) different from both test drugs.

Figure 8: Effect of compounds on intestinal motility following administration of SR1

The figure shows partial reversal of the effect of (+)-CBD-DMH (20 mg/kg) on intestinal motility by the CB<sub>1</sub> receptor antagonist SR141716A [Sanofi] (SR1, 1 mg/kg). SR1 was injected (i.p.) 30 min before the agonist. 60 min after (+)CBD-DMH the number of fecal pellets was recorded.

\*) Different from Vehicle+Vehicle ( $P < 0.05$ )

\*\*) Different from Vehicle+Vehicle ( $P < 0.01$ )

\*\*\*) Different from Vehicle+Vehicle ( $P < 0.001$ )

**Figure 9: Effect of compounds on intestinal motility following administration of SR2**

The figure shows that there was no reversal of the effect of (+)-CBD-DMH (20 mg/kg) on intestinal motility by the CB2 receptor antagonist SR144528 [Sanofi] (SR2, 1 mg/kg). SR2 was injected (i.p.) 30 min before the agonist. 60 min after (+)-CBD-DMH the number of fecal pellets was recorded.

- \*) Different from Vehicle+Vehicle ( $P < 0.05$ )
- \*\*) Different from Vehicle+Vehicle ( $P < 0.01$ )
- \*\*\*) Different from Vehicle+Vehicle ( $P < 0.001$ )

**Figure 10: Effects on intestinal motility in CB<sub>1</sub><sup>-/-</sup> knockout mice**

The figure shows that there were no effects of (+)-7-OH-CBD-DMH and (+)-CBD-DMH on intestinal motility in CB<sub>1</sub><sup>-/-</sup> knockout mice. Female CB<sub>1</sub><sup>-/-</sup> knockout mice were injected *i.p.* with (+)-7-OH-CBD-DMH, (+)-CBD-DMH or  $\Delta^9$ -THC (20 mg/kg). Intestinal motility (defecation rate) was recorded for a period of 3 h. No significant effects were observed for any compound.

**Detailed Description of the Invention**

In search for selective modulators of the peripheral cannabinoid system, the inventors tested a series of cannabidiol analogues for their *in vivo* central as well as peripheral activity. Central activity was assessed in the "tetrad" which is a series of assays commonly used to measure central cannabimimetic effects [Martin et al., 1991; Fride and Sanuco-Pena 2002]. Three parameters for peripheral activity were used: since gastrointestinal transit is regulated locally in the periphery rather than by centrally located CB<sub>1</sub> receptors [Izzo et al., 2000; Landi et al., 2002], intestinal motility was used as one parameter of peripheral cannabinoid effects which was measured as rates of defecation. As demonstrated in the following Examples, central and peripheral effects of cannabidiol (CBD) analogues can be conveniently distinguished using this paradigm.

In addition, *in vivo* inflammatory responsiveness to arachidonic acid-induced inflammation of the external ear [Young et al., 1984; Hanus et al., 1999] was tested. With this method it was shown thus far that (+) CBD-DMH is as effective as indomethacin in preventing swelling of the ear. In a separate experiment, (+)-7OH-CBD-DMH also effectively prevented ear inflammation.

As mentioned in the Background of the Invention, it was previously reported [Bisogno et al., 2001], that the (+)-CBD analogues have a strong affinity for the CB<sub>1</sub> receptor (e.g. (+)-7-OH-CBD-DMH,  $K_d=2.5\pm0.03$ nM; (+)-CBD DMH,  $K_d=17.4\pm1.8$ nM) and, more modestly, for the CB<sub>2</sub> receptor [(+)-7-OH-CBD-DMH:  $K_d=44$ nM $\pm$ 3.1nM; (+)-CBD-DMH:  $K_d=211\pm23$ nM] (see also Table I). However, significant and consistent central activity was observed only with (+)-7OH-CBD-DMH, while the other (+)-CBD derivatives only exhibited spurious or no central effects at all. All compounds, however, potently inhibited defecation over a prolonged period (4 hr) without inducing hypothermia (a measure of central activity), thus excluding a delayed psychoactive effect. Moreover, (+)-CBD-DMH was of equal potency as indomethacin in preventing arachidonic acid-induced inflammation of the external ear. Finally, this compound also completely inhibited the second phase of formalin-induced peripheral pain, while it was not active in the hot plate test, a centrally mediated pain response [Tjolsen et al., 1992].

The inhibitory effect of both (+)-7-OH-CBD-DMH and (+)-CBD-DMH on defecation was effectively antagonized by the CB<sub>1</sub> antagonist (SR141716A), but not at all by the CB<sub>2</sub> antagonist (SR144528), suggesting that (+)-CBD-DMH partly or fully inhibited defecation *via* CB<sub>1</sub> receptors. This conclusion was strengthened by the absence of inhibition of intestinal motility in CB<sub>1</sub><sup>-/-</sup> receptor knockout mice.

Since it is unlikely that (+)-CBD-DMH does not cross the blood brain barrier, while its 7-OH-counterpart does, without being bound by theory, it may be suggested that (+)-CBD-DMH is devoid of central effect because it may have antagonist or partial agonist/antagonist properties in the central nervous system, while acting as an agonist in intestinal tissue and possibly other tissues, which may be in accord with other publications. For example, tissue-specific distribution of partial agonist/antagonist properties of the same compound has been thoroughly documented for benzodiazepines and muscarinic ligands [Haefely et al., 1990, Gardner, 1988; Gurwitz et al., 1994].

Although (+)-7-OH-CBD-DMH and (+)-CBD-DMH bind to CB<sub>2</sub> receptors [Bisogno et al., 2001], the complete lack of antagonism by 1 or 3 mg/kg SR144528 of the effects of the (+)-CBD analogues on defecation, excludes mediation by CB<sub>2</sub> receptors. Alternative receptor mechanisms include VR1 receptors. Since the VR1 receptor antagonist capsazepine did not affect anandamide-induced intestinal immotility [Izzo et al., 2001], the VR1 receptor is unlikely to play such role. Further, since the CBD analogues, except (+)-CBD, did not stimulate VR1 receptors [Bisogno et al., 2001], mediation *via* VR1 receptors is excluded. Moreover, the inventors have shown that indeed, capsazepine did not affect the inhibition of defecation induced by (+)-CBD-DMH or (+)-7-OH-CBD-DMH (data not shown).

In conclusion, the inventors have shown that of a series of (+)-CBD analogues, all of which bind CB<sub>1</sub> and to a lesser extent CB<sub>2</sub> receptors, all except (+)-CBD itself, inhibit intestinal activity. These observations indicate that the two analogues ((+)-CBD-DMH and (+)-7-OH-CBD-DMH), inhibited defecation, at least in part, *via* CB<sub>1</sub> receptors. Further, the inventors have shown the antiinflammatory and analgesic capacity of these compounds in the periphery. But for (+)-7-OH-CBD-DMH, none of

the (+)-CBD analogues had central activity. It may be suggested that (+)-CBD-DMH, (+)-7-OH-CBD, (+)-COOH-CBD and (+)-COOH-CBD-DMH have partial agonist/antagonist effects in the central nervous system, but agonist properties in intestinal tissue. In addition, especially the acids, may not be able to cross the blood-brain barrier, thereby being prevented from exerting a central effect. Therefore these (+)-CBD analogues, *via* CB<sub>1</sub> receptors intestine-relaxing and antiinflammatory/peripheral pain activities, may be developed as cannabinoid-based medicinal drugs for peripheral conditions such as inflammatory bowel disease, diarrhea and inflammatory pain.

Thus, the invention relates to use of a compounds of formula Ia, wherein the substituents are as defined above, as CB<sub>1</sub> receptor partial agonist or antagonist in the central nervous system, but CB<sub>1</sub> agonist in the peripheral system, particularly the intestines.

The invention further relates to use of centrally inactive (+)CBD analogues as antidiarrheal, antiinflammatory and analgesic drugs for the gastrointestinal system and other peripheral systems.

Particularly preferred compounds are (+)-CBD-DMH, (+)-COOH-CBD and (+)-COOH-CBD-DMH.

The invention also relates to some novel (+)-CBD derivatives.

The invention will be described in more detail on hand of the following Examples, which are illustrative only and do not in any sense limit the invention, which is defined by the appended claims.

## Examples

### **Materials and methods**

#### *2.1 Mice*

Female Sabra mice (2-3 months of age) were purchased from Harlan, Israel. Breeding pairs of CB<sub>1</sub><sup>-/-</sup> receptor knockout mice were provided by Prof. A. Zimmer, University Clinic Bonn, Germany.

#### *2.2 Drugs*

All (cannabidiol-derived) compounds were prepared in the inventors' laboratory (Department of Medicinal Chemistry and Natural Products, Hebrew University of Jerusalem). The CB<sub>1</sub> and CB<sub>2</sub> receptor antagonists, SR141716A and SR144528, respectively, were kindly supplied by NIDA (Research Triangle). All compounds were prepared in a mixture of ethanol:cremophor (Sigma):saline=1:1:18 (see for example Fride and Mechoulam, 1993].

The synthesis of the (+)-CBD derivatives is schematically illustrated in Figs. 11a, 11B and 11C and in the following synthetic Examples.

In the following synthesis Examples the numbers of compounds in brackets are as indicated in Figs. 11A, 11B and 11C.

#### Example 1

##### **(+)-Dimethoxy-CBD (4a)**

(+)-CBD (1a), (3g, 9.95 mmol) was dissolved in DMF (55 ml). K<sub>2</sub>CO<sub>3</sub> (7.35g, 53.3 mmol) and CH<sub>3</sub>I (2.3 ml, 36.9 mmol) were added and the mixture was stirred at room temperature for 4 hours. The reaction was monitored by TLC (10% Ether/P. E.) till the starting material was disappeared. Then 200ml of water were added and the solution was



extracted with Ether. The organic phase was washed with brine till neutral pH, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvent under reduced pressure afforded 3.2 g of the product (yield 98%).

(4a):  $^1\text{H-NMR}$   $\delta$  6.344 (2H, s, Ar), 5.220 (1H, s, olefin), 4.460-4.436 (2H, d,  $J=7.2$  Hz), 4.023-3.971 (1H, m, benzyl), 3.741 (6H, s,  $\text{OCH}_3$ ), 2.960-2.869 (1H, td,  $J=11.5, 4.5$  Hz, allyl), 2.717-2.569 (2H, t,  $J=7.5$  Hz, benzyl), 2.259-2.144 (1H, m), 2.018-1.960 (1H, m), 1.789-1.722 (1H, m), 1.678 (3H, s, allyl  $\text{CH}_3$ ), 1.568 (6H, br s), 1.352 (4H, m) 0.936-0.890 (3H, t,  $J=6.8$  Hz, terminal  $\text{CH}_3$ ).

IR: 2875, 1600, 1570, 1440, 1410, 1220, 1100, 880  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +96.8° (c 12.19 mg/ml,  $\text{CHCl}_3$ )

#### Example 2

##### **(+)-Dimethoxy-CBD-DMH (4b)**

Prepared with the same procedure reported for (4a), with (+)-CBD-DMH as starting material.

(4b):  $^1\text{H-NMR}$   $\delta$  6.449 (2H, s, Ar), 5.238 (1H, s, olefin), 4.422-4.382 (2H, d,  $J=12.0$

Hz), 4.120-3.901 (1H, m, benzyl), 3.784 (6H, s,  $\text{OCH}_3$ ), 2.933-2.801 (1H, m, benzyl), 2.270-2.086 (1H, m, allyl), 2.048-1.924 (1H, m), 1.781-1.501 (10H, m), 1.253-1.185 (10H, m), 1.105-0.962 (2H, m) 0.849-0.8816 (3H, t,  $J=6.8$  Hz, terminal  $\text{CH}_3$ ).

IR : 2900, 1600, 15780, 1440, 1400, 1100  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +98.1° (c 2.04 mg/ml,  $\text{CHCl}_3$ )

### Example 3

#### **(+)-1,2 Oxido-dimethoxy-hexahydrocannabinol (5a)**

3-Chloro-perbenzoic acid (70% pure 1.2 g, 4.85 mmol) was dissolved in 50 ml  $\text{CH}_2\text{Cl}_2$  and the solution was cooled to  $0^\circ\text{C}$ . A solution of (4a) (1.65 g, 4.82 mmol) in 10ml  $\text{CH}_2\text{Cl}_2$  was slowly injected. The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min and monitored by TLC (10% Ether/P. E.). The reaction was quenched by addition of a saturated aqueous solution of  $\text{NaHCO}_3$  and the organic phase was separated by a separatory funnel, then the aqueous phase was extracted with ether. The combine organic extracts were washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded a residue that was flash chromatographed (7% Ether/P. E) to give the epoxy-derivative (5a) (yield 65%).

(5a) :  $^1\text{H-NMR}$   $\delta$  6.348-6.322 (2H, d,  $J=7.7$  Hz, Ar), 4.369 (1H, s, olefin), 4.159 (1H, s, olefin), 3.803 (3H, s,  $\text{OCH}_3$ ), 3.714 (3H, s,  $\text{OCH}_3$ ), 3.612-3.571 (1H, d,  $J=12.2$  Hz, H on epoxide ring), 2.574-2.522 (2H, t,  $J=7.9$  Hz, benzyl), 2.293-2.201 (1H, m), 2.081-1.995 (1H, m), 1.882-1.757 (1H, m), 1.628-1.585 (6H, m), 1.364-1.313 (9H, m), 0.936-0.890 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR : 2900, 1610, 1580, 1460, 1420, 1120, 760  $\text{cm}^{-1}$ .

### Example 4

#### **(+)-1,2 Oxidodimethoxyhexahydrocannabinol DMH (5b)**

Prepared with the same procedure reported for (5a), but the yield was slightly better (70%).

(5b):  $^1\text{H-NMR}$   $\delta$  6.466-6.442 (2H, d,  $J=7.2$  Hz, Ar), 4.358 (1H, s, olefin), 4.121 (1H, s, olefin), 3.805 (3H, s,  $\text{OCH}_3$ ), 3.719 (3H, s,  $\text{OCH}_3$ ), 3.591-3.555 (1H, d,  $J=10.8$  Hz, H on epoxide ring), 2.235-2.193 (1H, m, benzyl), 2.105-1.995 (1H, m, allyl), 1.907-1.761 (1H, m), 1.745-1.514 (10H, m), 1.369 (3H, s, allyl  $\text{CH}_3$ ), 1.268-1.180 (10H, m), 1.081-0.942 (2H, m.), 0.856-0.812 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1600, 1580, 1460, 1450, 1210, 1110, 750  $\text{cm}^{-1}$ .

#### Example 5

##### **(3S,4S)-3-[2,6-Dimethoxy-4-pentylphenyl]-2-hydroxy-4-isopropenyl-1-methylene cyclohexane (6a)**

Butyllithium in hexane (5.6 ml, 14 mmol) was added to a 0°C solution of N-cyclohexylisopropylamine (1.85 ml, 11.3 mmol) in anhydrous toluene (10 ml, distilled over sodium) under  $\text{N}_2$  atmosphere. After 15 min, methylmagnesium bromide in ether (3.8 ml, 11.4 mmol) was injected, and the reaction mixture was stirred for 45 min at room temperature. A solution of (5a) (1g, 2.79 mmol) in dry toluene (3 ml) was added, and the mixture was heated to 40°C and stirred for two hours. Then the reaction was cooled to 0°C and quenched by the slow addition of 5M HCl. The organic phase was separated by a separatory funnel, and then the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded a residue that on TLC (20% Ether/P. E.) showed only one spot, and by  $^1\text{H}$ -NMR was proved to be (6a) (yield 97%).

(6a):  $^1\text{H}$ -NMR  $\delta$  6.332 (2H, s, Ar), 5.083 (1H, s, olefin), 4.821 (1H, s, olefin), 4.662-4.622 (1H, d,  $J=11.8$  Hz, CHOH), 4.387 (1H, s, olefin), 4.379 (1H, s, olefin), 3.798 (3H, s,  $\text{OCH}_3$ ), 3.745 (3H, s,  $\text{OCH}_3$ ), 3.200-3.154 (1H, td,  $J=11.2, 3.0$  Hz, benzyl), 2.564-2.452 (3H, m), 2.255-1.625 (1H, m), 1.754-1.707 (1H, m), 1.609-1.350 (4H, m), 1.432 (3H, s, allyl  $\text{CH}_3$ ), 1.350-1.313 (4H, m), 0.924-0.878 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3400, 2920, 1590, 1450, 1120, 900, 730  $\text{cm}^{-1}$ .

$[\alpha]_D$ : -62.3° (c 15.36 mg/ml,  $\text{CHCl}_3$ )

#### Example 6

**(3S,4S)-3-[4-(1',1'-Dimethylheptyl)-2,6-dimethoxyphenyl]-2-hydroxy-4-isopropenyl-1-methylenecyclohexane (6b)**

Prepared with the same procedure reported for (6a).

(6b):  $^1\text{H-NMR}$   $\delta$  6.440 (2H, s, Ar), 5.080 (1H, s, olefin), 4.821 (1H, s, olefin), 4.655-4.621 (1H, d,  $J=9.0$  Hz, CHOH), 4.448 (1H, s, olefin), 4.338 (1H, s, olefin) 3.802 (3H, s,  $\text{OCH}_3$ ), 3.744 (3H, s,  $\text{OCH}_3$ ), 3.215-3.127 (1H, td,  $J=11.7, 3.0$  Hz, benzyl), 2.505-2.444 (1H, dt,  $J=12.6, 3.0$  Hz allyl), 2.255-2.182 (1H, td,  $J=9.0, 3.0$  Hz), 1.740-1.688 (2H, m), 1.555-1.423 (8H, m), 1.301-1.177 (10H, m), 1.025-0.955 (2H, m), 0.859-0.814 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3400, 2900, 1600, 1560, 1450, 1400, 1110, 750  $\text{cm}^{-1}$ .

$[\alpha]_D$ :  $-47.6^\circ$  (c 1.05 mg/ml,  $\text{CHCl}_3$ )

Example 7

**(3S,4s)-3-[2,6-Dimethoxy-4-pentylphenyl]-2-acetoxy-4isopropenyi-1-methylene-cyclohexane (7a)**

(6a) (0.9 g, 2.5 mmol) was dissolved in pyridine (2 ml) and acetic anhydride (2 ml) and the reaction was stirred for 18 hours at room temperature. Then the solution was poured onto iced water (20 ml) and extracted with ether. The combined organic extracts were washed successively with 1 N HCl, aqueous sodium bicarbonate and brine, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded an oily residue that on TLC (20% Ether/P. E.) showed only one spot, that by  $^1\text{H-NMR}$  was proved to be (7a) (yield ~100%).

(7a):  $^1\text{H-NMR}$   $\delta$  6.281-6.267 (2H, d,  $J=4.2$  Hz, Ar), 5.967-5.931 (1H, d,  $J=10.8$  Hz, olefin), 4.767-4.721 (2H, d,  $J=13.7$  Hz, olefin), 4.535 (1H, s, olefin), 4.419 (1H, s, olefin), 3.793 (3H, s,  $\text{OCH}_3$ ), 3.745 (3H, s,  $\text{OCH}_3$ ), 3.491-3.416 (1H, t,  $J=11.4$  Hz), 3.286-3.197 (1H, td,  $J=11.4, 2.7$  Hz, benzyl), 2.533-2.469 (2H, t,  $J=7.2$  Hz), 2.325-2.249 (1H, m), 1.717 (3H, s, OAc), 1.625-1.447 (6H, m), 1.404-1.250 (6H, m), 0.924-0.878 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 2910, 1750, 1450, 1360, 1240, 1120, 890  $\text{cm}^{-1}$ .

#### Example 8

##### **(3R,4R)-3-[4-(1',1'-Dimethylheptyl)-2,6-dimethoxyphenyl]-2-acetoxy-1-methylene-cyclohexane(7b)**

Prepared with the same procedure reported for (7a).

(7b):  $^1\text{H-NMR}$   $\delta$  6.409-6.377 (2H, d,  $J=8.1$  Hz, Ar), 5.980-5.931 (1H, d,  $J=14.5$  Hz, CHOAc), 4.768-4.717 (2H, d,  $J=15.2$  Hz, olefin), 4.521 (1H, s, olefin), 4.405 (1H, s, olefin), 3.802 (3H, s,  $\text{OCH}_3$ ), 3.754 (3H, s,  $\text{OCH}_3$ ), 3.268-3.181 (1H, m, benzyl), 2.522-2.459 (1H, m, allyl), 1.781-1.717 (1H, m), 1.695 (3H, s, OAc), 1.540-1.484 (6H, m), 1.239-1.171 (14H, m), 0.980-0.923 (2H, m), 0.854-0.809 (3H, t,  $J=6.7$  Hz, terminal  $\text{CH}_3$ ).

IR : 290,1750,1450,1360,1240,1120,880  $\text{cm}^{-1}$ .

#### Example 9

##### **(+)-7-Bromo-dimethoxy CBD (8a)**

(7a) (1g, 2.5 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (50 ml, distilled over  $\text{CaH}_2$ ) under nitrogen atmosphere and  $\text{TMSBr}$  (1.6 ml, 12.1 mmol) was added. The reaction was stirred at r. t. for 4 hours, then it was shaken with a saturated aqueous solution of  $\text{NaHCO}_3$  and the organic phase was separated by a separatory funnel, then the aqueous phase was extracted with ether. The combine organic extracts were washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvents afforded a residue that  $^1\text{H-NMR}$  and TLC (20% Ether/P. E.) showed predominantly a single component, that was used immediately with no purification.

(8a) :  $^1\text{H-NMR}$   $\delta$  6.322 (2H, s, Ar), 5.736 (1H, s, olefin), 4.767 (1H, s, olefin), 4.454, 4.535 (1H, s, olefin), 4.006 (2H, s,  $\text{CH}_2\text{Br}$ ), 3.736 (6H, s,  $\text{OCH}_3$ ), 2.853-2.767 (1H, td,  $J=11.9, 3.2$  Hz, benzyl), 2.565-2.512 (1H, t,  $J=7.9$  Hz, benzyl), 2.397-2.359 (1H, m), 2.277-2.183 (1H, m), 1.870-1.662 (2H, m), 1.619 (3H, s, allyl  $\text{CH}_3$ ), 1.439-1.237 (7H, m), 0.928-0.882 (3H, t,  $J=6.6$  Hz, terminal  $\text{CH}_3$ ).

IR : 2900, 1580, 1460, 1230, 1120  $\text{cm}^{-1}$ .

Example 10

**(+)-7-Bromo-dimethoxy CBD DMH (8b)**

Prepared with the same procedure reported for (8a).

(8b):  $^1\text{H-NMR}$   $\delta$  6.431 (2H, s, Ar), 5.602 (1H, s, olefin), 4.821-4.337 (4H, m,  $\text{CH}_2\text{Br}$  + olefin), 4.042-3.961 (1H, m, olefin), 3.720 (6H, s,  $\text{OCH}_3$ ), 3.116-3.010 (1H, m, benzyl), 2.842-2.762 (1H, allyl), 1.782-1.517 (9H, m), 1.247-1.178 (10H, m), 1.010 (2H, br s), 0.831 (3H, br s, terminal  $\text{CH}_3$ ).

IR: 2910, 1580, 1460, 1230, 1120  $\text{cm}^{-1}$ .

Example 11

**(+)-7-Acetoxy-dimethoxy CBD (9a)**

(8a) (570 mg, 1.35 mmol) was dissolved in acetone (15ml, stored on  $4\text{\AA}^\circ$  molecular sieves) and tetrabutylammonium acetate (450mg, 1.49 mmol). The mixture was stirred, refluxed and monitored by TLC (20% Ether/P. E.). After 2 hours there was no more starting material. The acetone was removed under reduced pressure, and the residue was diluted with water (20 ml) and extracted with ether. The combine organic extracts were washed with aqueous sodium bicarbonate and brine, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded 520 mg of an oily residue (96% yield).

(9a) :  $^1\text{H-NMR}$   $\delta$  6.320 (2H, s, Ar), 5.581 (1H, s, olefin), 4.492-4.386 (4H, m,  $\text{CH}_2\text{OAc}$  + olefin), 4.040-3.986 (1H, m, benzyl), 3.715 (6H, s,  $\text{OCH}_3$ ), 2.853-2.801 (1H, m), 2.195-2.071 (2H, m), 2.060 (3H, s, OAc), 1.823-1.695 (2H, m), 1.605 (5H, br s), 1.323 (4H, br s), 0.921-0.875 (3H, t,  $J=6.7$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1720, 1580, 1440, 1110  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +135.  $2^\circ$  (c 15.95 mg/ml,  $\text{CHCl}_3$ )

Example 12**(+)-7-Acetoxy-dimethoxy CBD DMH (9b)**

Prepared with the same procedure reported for (9a), but the yield was slightly worse (90 %).

(9b):  $^1\text{H-NMR}$   $\delta$  6.440 (2H, s, Ar), 5.609 (1H, s, olefin), 4.498-4.343 (4H, m,  $\text{CH}_2\text{OAc}$  + olefin), 4.041-3.965 (1H, m, benzyl), 3.719 (6H, s,  $\text{OCH}_3$ ), 2.845-2.763 (1H, m, allyl), 2.193-2.099 (2H, m), 2.061 (3H, s, OAc), 1.796-1.776 (2H, m), 1.594-1.518 (7H, m), 1.254-1.179 (10H, m), 1.015 (2H, brs), 0.856-0.861 (3H, t,  $J=6.4$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1720, 1600, 1580, 1450, 1410, 1220  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +90.5 (c 2.53 mg/ml,  $\text{CHCl}_3$ )

Example 13**(+)-7-Hydroxy-dimethoxy CBD (10a)**

(9a) (500 mg, 1.25 mmol) was dissolved in ethanol (20ml) and NaOH 1N (2 ml) was added and the reaction was refluxed for 1 hour. The ethanol was removed under reduced pressure, and the residue was diluted with water (20 ml) and HCl 2N was added till acid pH. The solution was extracted with ether. The combine organic extracts were washed brine, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded 430 mg of an oily residue (96% yield).

(10a):  $^1\text{H-NMR}$   $\delta$  6.328 (2H, s, Ar), 5.510 (1H, s, olefin), 4.458-4.414 (2H, d,  $J=13.2$  Hz, olefin), 4.010 (2H, br s,  $\text{CH}_2\text{OH}$ ), 3.728 (6H, s,  $\text{OCH}_3$ ), 2.858-2.806 (1H, m, benzyl), 2.566-2.508 (2H, t,  $J=7.5$  Hz, benzyl), 2.213 (2H, m), 1.817-1.582 (7H, m), 1.451-1.259 (5H, m), 0.924-0.878 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1580, 1440, 1220, 1110  $\text{cm}^{-1}$ .

MS  $m/z$  (relative intensity): 358 ( $\text{M}^+$ , 7), 327 (52), 290 (80), 221 (100), 152 (33).

Exact mass calculated for  $\text{C}_{25}\text{H}_{38}\text{O}_3$ : 358.25080, found 358.2511.

Example 14**(+)-7-Hydroxy-dimethoxy CBD DMH (10b)**

Prepared with the same procedure reported for (10a).

(10b):  $^1\text{H-NMR}$   $\delta$  6.446 (2H, s, Ar), 5.528 (1H, s, olefin), 4.434-4.367 (2H, d,  $J=20.1$  Hz, olefin), 4.010 (3H, br s,  $\text{CH}_2\text{OH} + \text{OH}$ ), 3.729 (6H, s,  $\text{OCH}_3$ ), 2.905-2.785 (1H, m, benzyl), 2.248-2.105 (2H, m), 1.759-1.704 (2H, m), 1.535 (3H, s, allyl  $\text{CH}_3$ ), 1.495-1.460 (4H, m) 1.360-1.120 (10H, m) 0.980-0.9875 (2H, m), 0.797-0.752 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1600, 1570, 1420, 1400, 1230, 1110, 750  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +135. 2° (c 15.95 mg/ml,  $\text{CHCl}_3$ )

MS  $m/z$  (relative intensity): 414 ( $\text{M}^+$ , 14), 396 (8), 383 (100), 346 (43), 277 (50), 119 (7).

Exact mass calculated for  $\text{C}_{27}\text{H}_{42}\text{O}_3$ : 358.31340, found 358.3136.

Example 15**(+)-7-Hydroxy CBD (2a)**

A Grignard reagent was prepared with magnesium (100 mg, 4.17 mmol) and  $\text{CH}_3\text{I}$  (0.26 ml, 4.17 mmol) in dry ether (3ml, distilled over sodium) under  $\text{N}_2$  atmosphere. (10a) (420 mg, 1.17 mmol) in ether (1 ml) was slowly added to the stirred solution and the ether was distilled off. The residue was heated under  $\text{N}_2$  atmosphere till 210° C for 45 min. Then the flask was cooled till room temperature and the reaction was quenched with ice water. The aqueous solution was extracted with ether several times. The combine organic extracts were dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded a residue that was chromatographed on silica gel (25% Ether/P. E.) to give 150 mg of the pure (2a) (yield 40 %).

(2a):  $^1\text{H-NMR}$   $\delta$  6.200 (2H, s, Ar), 5.822 (1H, s, olefin), 4.629 (1H, s, olefin), 4.518 (1H, s, olefin), 4.075 (2H, s,  $\text{CH}_2\text{OH}$ ), 3.962-3.923 (1H, m, benzyl), 2.567-2.484 (1H, td,  $J=13.3, 2.7$  Hz, allyl), 2.435-2.384 (2H, t,  $J=7.5$  Hz, benzyl), 1.882-1.734 (2H, m), 1.660 (6H, s, allyl  $\text{CH}_3$ ), 1.584-



1.487 (2H, m), 1.285-1.248 (6H, m), 0.886-0.843 (3H, t,  $J=6.3$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1620, 1580, 1440, 1240, 1020, 730  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +67. 3° (c 19.51 mg/ml,  $\text{CHCl}_3$ )

MS  $m/z$  (relative intensity): 330 ( $M^+$ , 10), 312 (44), 299 (53), 284 (44), 244 (100), 231 (56), 187 (29), 147 (13).

Exact mass calculated for  $\text{C}_{21}\text{H}_{30}\text{O}_3$ : 330.21949, found 330.2231.

#### Example 16

##### **(+)-7-Hydroxy CBD-DMH (2b)**

Prepared with the same procedure reported for (2a).

(2b):  $^1\text{H-NMR}$   $\delta$  6.335 (2H, s, Ar), 5.863 (1H, s, olefin), 4.652 (1H, s, olefin), 4.538 (1H, s, olefin), 4.108 (2H, s,  $\text{CH}_2\text{OH}$ ), 3.920-3.889 (1H, d,  $J = 9.3$  Hz, benzyl), 2.498-2.433 (1H, m, allyl), 2.228 (2H, br s), 2.064-1.715 (2H, m), 1.648-1.428 (7H, m), 1.312-1.168 (12H, m), 0.853-0.808 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1620, 1580, 1420, 1210, 1020, 750  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +61. 1° (c 1.8 mg/ml,  $\text{CHCl}_3$ )

MS  $m/z$  (relative intensity): 386 ( $M^+$ , 24), 369 (30), 368 (30), 355 (100), 300 (43), 287 (510), 283 (34), 249 (38), 233 (22), 187 (10).

Exact mass calculated for  $\text{C}_{25}\text{H}_{38}\text{O}_3$ : 386.28210, found 386.2825.

#### Example 17

##### **(3S, 4S)-3- [2, 6-Dihydroxy-4-pentylphenyl]-2-hydroxy-4-isopropenyl-1-methylene cyclohexane (11a)**

A Grignard reagent was prepared with magnesium (84 mg, 3.5 mmol) and  $\text{CH}_3\text{I}$  (0.2ml, 3.5 mmol) in dry ether (1 ml, distilled over sodium) under  $\text{N}_2$  atmosphere. (6a) (360 mg, 1 mmol) in ether (0.5 ml) was added to the stirred solution and the ether was distilled. The residue was heated under  $\text{N}_2$  atmosphere till 210° C for 45 min.

Then the flask was cooled till room temperature and the reaction was quenched with ice water. The aqueous solution was extracted several times with ether. The combined organic extracts were dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded a residue that was chromatographed on silica gel (25% Ether/P. E.) to give 132 mg of the pure (11a) (yield 40 %).

(11a):  $^1\text{H-NMR}$   $\delta$  6.156-6.097 (2H, d,  $J=17.7$  Hz, Ar), 5.612 (1H, s, OH), 5.370 (1H, s, OH), 5.092 (1H, s, olefin), 4.847 (1H, s, olefin), 4.684-4.625 (2H, m, CHOH + olefin), 4.462 (1H, s, olefin), 3.300-3.205 (1H, td,  $J=12.7, 2.7$  Hz, benzyl), 3.128-3.058 (1H, t,  $J=10.5$ , Hz, allyl), 2.270-2.141 (1H, m), 2.122-2.049 (1H, br s, OH), 1.767-1.712 (1H, m), 1.534-1.48 (5H, m), 1.290-1.183 (4H, m), 0.895-0.881 (3H, t,  $J=6.6$  Hz, terminal  $\text{CH}_3$ ).  
IR: 3350, 2900, 1620, 1580, 1420, 1160, 1000, 750  $\text{cm}^{-1}$ .

#### Example 18

(3S,4S)-3-[4-(1',1'-Dimethylheptyl)-2,6-dihydroxyphenyl]-2-hydroxy-4-isopropenyl-1-methylenecyclohexane (11b)

Prepared with the same procedure reported for (11a), but the yield was slightly better (45%).

(11b):  $^1\text{H-NMR}$   $\delta$  6.295 (1H, s, Ar), 6.229 (1H, s, Ar), 5.786 (1H, s, OH), 5.546 (1H, s, OH), 5.127 (1H, s, olefin), 4.861 (1H, s, olefin), 4.751-4.716 (1H, d,  $J=3.3$  Hz, CHOH), 5.127 (1H, s, olefin), 4.444 (1H, s, olefin), 3.421-3.276 (1H, m, benzyl), 3.132-3.062 (1H, t,  $J=10.5$ , Hz, allyl), 2.502-2.459 (1H, d,  $J=12.9$  Hz), 2.251-2.175 (2H, m), 1.780-1.739 (1H, m), 1.528 (3H, s, allyl  $\text{CH}_3$ ) 1.460-1.433 (4H, m), 1.251-1.170 (10H, m), 0.954 (2H, br s) 0.845 (3H, br s, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1620, 1580, 1410, 1210, 750  $\text{cm}^{-1}$ .

$[\alpha]_D$ : -47.3° (c 1.48 mg/ml,  $\text{CHCl}_3$ )

Example 19

(3S,4S)-3- [2,6-Diacetoxy-4-pentylphenyl]-2-acetoxy-4-isopropenyl-1-methylene-cyclohexane (12a)

(11a) (100 mg, 0.3 mmol) was dissolved in pyridine (0.5 ml) and acetic anhydride (0.5 ml) and the reaction was stirred for 18 hours at room temperature. Then the solution was poured onto iced water (10 ml) and extracted with ether. The combine organic extracts were washed successively with 1 N HCl, aqueous sodium bicarbonate and brine, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded 136 mg of an oily residue that by NMR was proved to be (12a) (yield -100%).

(12a):  $^1\text{H-NMR}$   $\delta$  6.861 (1H, s, Ar), 6.696 (1H, s, Ar), 5.725-5.688 (1H, d,  $J=11.1$  Hz, CHOAC), 4.083 (1H, s, olefin), 4.689 (1H, s, olefin), 4.540-4.515 (2H, d,  $J=7.5$  Hz, olefin), 3.180-3.105 (1H, t,  $J=11.3$  Hz, benzyl), 2.893-2.802 (1H, td,  $J=11.3, 3.2$  Hz, allyl), 2.563-2.513 (2H, t,  $J=7.5$  Hz, benzyl), 2.374 (3H, s, OAc), 2.280 (3H, s, OAc), 1.798 (3H, s, OAc), 1.614-1.470 (5H, m), 1.286-1.246 (8H, m), 0.886-0.844 (3H, t,  $J=6.3$  Hz, terminal  $\text{CH}_3$ ).

IR: 2910, 1750, 1410, 1350, 1180, 1130, 890  $\text{cm}^{-1}$ .

Example 20

(3S,4S)-3-[2,6-Diacetoxy-4-(1',1'-dimethylheptyl)-phenyl]-2-acetoxy-4-isopropenyl-1-methylenecyclohexane (12e)

Prepared with the same procedure reported for (12a).

(12b):  $^1\text{H-NMR}$   $\delta$  6.947 (1H, s, Ar), 6.795 (1H, s, Ar), 5.732-5.695 (1H, d,  $J=11.0$  Hz, CHOAC), 4.798 (1H, s, olefin), 4.691 (1H, s, olefin), 4.540-4.515 (2H, d,  $J=7.5$  Hz, olefin), 3.167-3.095 (1H, t,  $J=11.3$  Hz, benzyl), 2.854-2.816 (1H, m, allyl), 2.561-2.515 (1H, d,  $J=13.8$  Hz, benzyl), 2.372 (3H, s, OAc), 2.287 (3H, s, OAc), 2.230-2.195 (1H, m), 1.825-1.770 (4H, m), 1.538-

1.424 (6H, m), 1.224-1.151 (12H, m), 0.955-0.945 (2H, m) 0.840-0.799 (3H, t,  $J=6.1$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1750, 1410, 1360, 1180, 1130, 890  $\text{cm}^{-1}$ .

#### Example 21

##### **(+)-7-Bromo-diacetate CBD (13a)**

(12a) (100 mg, 0.2 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (10 ml, distilled over  $\text{CaH}_2$ ) under nitrogen atmosphere.  $\text{TMSBr}$  (0.13 ml, 1 mmol) and  $\text{ZnI}_2$  (3.4 mg, 0.01 mmol) were added. The reaction was stirred at r. t. for 4 hours, then it was shaken with a saturated aqueous solution of  $\text{NaHCO}_3$  and the organic phase was separated by a separatory funnel, then the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvents afforded a residue that was used immediately with no purification.

(13a):  $^1\text{H-NMR}$   $\delta$  6.764 (2H, s, Ar), 5.456 (1H, s, olefin), 4.901 (1H, s, olefin), 4.752 (1H, s, olefin), 3.930- 3.903 (2H, m,  $\text{CH}_2\text{Br}$ ), 3.784-3.756 (1H, d,  $J=8.2$  Hz, benzyl), 2.592-2.643 (2H, m), 2.306 (6H, s, OAc), 2.198-2.131 (2H, t,  $J=10.2$  Hz), 1.708 (3H, s, allyl  $\text{CH}_3$ ), 1.698-1.472 (4H, m), 1.439-1.194 (5H, m), 0.090-0.865 (3H, t,  $J=5.3$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1750, 1360, 1200, 1020, 900, 720  $\text{cm}^{-1}$ .

#### Example 22

##### **(+)-7-Bromo-diacetate CBD DMH (13b)**

Prepared with the same procedure reported for (13a).

(13b):  $^1\text{H-NMR}$   $\delta$  6.816 (2H, s, Ar), 5.645 (1H, s, olefin), 4.557 (1H, s, olefin), 4.448 (1H, s, olefin), 4.016-3.966 (2H, m,  $\text{CH}_2\text{Br}$ ), 3.483-3.405 (1H, m, benzyl), 2.655-2.459 (1H, m, allyl), 2.220 (6H, s, OAc), 1.883-1.637 (4H, m), 1.510 (3H, s, allyl  $\text{CH}_3$ ), 1.485-1.426 (4H, m), 1.410-1.176 (10H, m), 1.010-0.995 (2H, m) 0.853-0.807 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1750, 1370, 1220, 1020, 900, 750  $\text{cm}^{-1}$ .

### Example 23

#### **(+)-7-Nor-formyl-diacetate CBD (14a)**

(13a) (100 mg, 0.21 mmol), 18-Crown-16 (55.4 mg, 0.21 mmol) and  $\text{K}_2\text{CrO}_4$  (50.9 mg, 0.26 mmol) were dissolved in anhydrous HMPT (2 ml, distilled under vacuum and stored over 4A° molecular sieves). The mixture was stirred and heated at 110 C for 2 hours. The reaction was cooled and quenched by addition of 1 M HCl and the aqueous phase was extracted with ether. The organic phase was washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvent under reduced pressure afforded a residue that was chromatographed on silica gel (20% Ether/PE.) to give 27.7 mg of the pure (14a) (yield 32 %).

(14a):  $^1\text{H-NMR}$   $\delta$  9.434 (1Hs CHO), 6.778 (2H, s, Ar), 6.638 (1H, s, olefin), 4.633 (1H, s, olefin), 4.489 (1H, s, olefin), 3.746-3.718 (1H, d,  $J=8.4$  Hz, benzyl), 2.686-2.552 (4H, m), 2.304-2.075 (6H, br s), 1.965-1.921 (1H, m), 1.754-1.590 (6H, m), 1.318-1.305 (5H, m), 0.909-0.865 (3H, t,  $J=6.2$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1750, 1670, 1160, 1020  $\text{cm}^{-1}$

$[\alpha]_D$ : +111.5 (c 3.5 mg/ml,  $\text{CHCl}_3$ )

### Example 24

#### **(+)-7-Nor-formyl-diacetate CBD DMH (14b)**

Prepared with the same procedure reported for (14a), but the yield was slightly worse (28 %).

(14b):  $^1\text{H-NMR}$   $\delta$  9.420 (1Hs CHO), 6.861 (2H, s, Ar), 6.501 (1H, s, olefin), 4.611 (1H, s, olefin), 4.455 (1H, s, olefin), 3.705-3.671 (1H, m, benzyl), 2.667-2.552 (3H, m), 2.292-2.071 (6H, br s, OAc), 1.960-1.890 (2H, m), 1.601 (3H, s, allyl  $\text{CH}_3$ ), 1.590-1.485 (4H, m), 1.241-1.711 (8H, m) 1.100-0.931 (2H, m) 0.854-0.865 (3H, t,  $J=5.7$  Hz, terminal  $\text{CH}_3$ ).

IR: 2900, 1750, 1660, 1160, 1020  $\text{cm}^{-1}$ .

$[\alpha]_D$ : +85.7° (c 1.4 mg/ml,  $\text{CHCl}_3$ )

#### Example 25

##### **(+)-7-Nor-carboxy-diacetate CBD (15a)**

$\text{NaClO}_2$  (80% pure 82.6 mg, 0.73 mmol) was added in small quantities to a stirred mixture of (14a) (70 mg, 0.17 mmol), 2-methyl-2-butene (0.45 ml, 4.25 mmol), a saturated aqueous solution of  $\text{KH}_2\text{PO}_4$  (0.2 ml) in t-butanol (4 ml). The reaction was stirred at room temperature for 5 hours, and monitored by TLC (50% Ether/P. E.). Then water was added (20 ml) and the mixture was extracted several times with ethyl acetate. The organic phase was washed with brine, dried over  $\text{MgSO}_4$  and filtered. Removal of the solvent under reduced pressure afforded a residue that was chromatographed on silica gel (30% Ether\PE.) to give 61.8 mg of the (15a) (yield 85%).

(15a):  $^1\text{H-NMR}$   $\delta$  6.939 (1H, s, olefin), 6.770 (2H, s, Ar), 4.611 (1H, s, olefin), 4.462 (1H, s, olefin), 3.618-3.718 (1H, m, benzyl), 2.589-2.538 (3H, m, allyl + benzyl), 2.212 (6H, s, OAc), 1.961-1.862 (1H, m), 1.858-1.641 (1H, m), 1.592 (5H, br s), 1.321-1.255 (7H, m), 0.903-0.858 (3H, t,  $J=6.8$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1750, 1270, 1020  $\text{cm}^{-1}$ .

#### Example 26

##### **(+)-7-Nor-carboxy-diacetate CBD DMH (15b)**

Prepared with the same procedure reported for (15a).

(15b):  $^1\text{H-NMR}$   $\delta$  6.946 (1H, s, olefin), 6.854 (2H, s, Ar), 4.592 (1H, s, olefin), 4.436 (1H, s, olefin), 3.635-3.590 (1H, m, benzyl), 2.605-2.455 (1H, m, allyl), 2.208 (6H, s, OAc), 1.950-1.803 (2H, m), 1.795-1.610 (2H, m), 1.574 (3H, s, hallyl  $\text{CH}_3$ ), 1.529-1.475 (4H, m), 1.267-1.174 (10H, m), 1.022 (2H, br s), 0.845-0.805 (3H, t,  $J=6.6$  Hz, terminal  $\text{CH}_3$ ).

IR: 3300, 2900, 1750, 1270, 1020  $\text{cm}^{-1}$ .

Example 27**7-Nor-carboxy CBD (3a)**

(15a) (50 mg, 0.12 mmol) was dissolved in ethanol (10ml) and 1N NaOH (0.5 ml) was added and the reaction was refluxed for 1 hour. The ethanol was removed under reduced pressure, and the residue was diluted with water (20 ml) and the mixture was acidified with 2N HCl. The solution was extracted with ether. The combine organic extracts were washed brine, dried on  $\text{MgSO}_4$  and filtered. Removal of the solvents under reduced pressure afforded a residue that was chromatographed on silica gel (30% Ether\PE.) to give 38.2 mg of the (3a) (yield 95%).

(3a):  $^1\text{H-NMR}$   $\delta$  7.085 (1H, s, olefin), 6.173 (2H, s, Ar), 4.604-4.566 (2H, d,  $J=11.4$  Hz, olefin), 4.115-4.033 (1H, m, benzyl), 2.799-2.688 (1H, m, allyl), 2.623-2.541 (1H, m), 2.444-2.391 (2H, t,  $J=7.5$  Hz), 1.950-1.869 (1H, m), 1.803-1.669 (5H, m), 1.623-1.453 (4H, m), 1.309-1.178 (5H, m), 0.902-0.857 (3H, t,  $J=6.5$  Hz, terminal  $\text{CH}_3$ ).

IR: 3350, 2950, 1700, 1440, 1400, 1160, 920, 740  $\text{cm}^{-1}$ .

$[\alpha]_D^{25} +112.3^\circ$  (c 1.87 mg/ml, MeOH)

Example 28**(+)-7-Nor-carboxy CBD DMH (3b)**

Prepared with the same procedure reported for (3a).

(3b):  $^1\text{H-NMR}$   $\delta$  7.121 (1H, s, olefin), 6.291 (2H, s, Ar), 4.619-4.555 (2H, d,  $J=19.1$  Hz, olefin), 4.036-4.033 (1H, d,  $J=8.9$  Hz, benzyl), 2.718-2.567 (2H, m), 2.378-2.274 (1H, m), 1.948-1.904 (1H, m), 1.828-1.765 (1H, m), 1.648 (3H, s, allyl  $\text{CH}_3$ ) 1.622-1.430 (4H, m), 1.236-1.189 (8H, m), 1.001-0.965 (2H, m), 0.878-0.837 (3H, t,  $J=6.2$  Hz, terminal  $\text{CH}_3$ ).

IR: 3330, 2900, 1700, 1420, 1160, 920, 740  $\text{cm}^{-1}$ .

$[\alpha]_D^{25} +86.7^\circ$  (c 2.05 mg/ml,  $\text{CHCl}_3$ )

## 2.3 Procedure

### Central activity

Mice were injected with antagonist 90 min before testing and/or with agonist 60 min before testing in a series of four assays which reflect central cannabinoid activity [Martin et.al, 1991, modified by Fride and Mechoulam, 1993]. This "tetrad" consists of, consecutively, ambulation and rearing in an open field (8 min), immobility on an elevated ring of 5 cm diameter (4 min), rectal temperature (Yellow Springs Instruments, Yellow Springs, OH, USA).

### Peripheral activity

a. *Intestinal motility* (defecation: the number of fecal pellets voided in the open field)

In some experiments (as indicated below), fecal pellets and body temperature were assessed for a prolonged period (3 hr).

b. *Arachidonic acid induced inflammation of the external ear*

Ear inflammation was measured by assessing ear tissue swelling after topical application of arachidonic acid, as described previously [Hanus et al., 1999]. Briefly, at various times after i.p. drug injections, arachidonic acid was applied to the inner surface of one ear (4.5 mg dissolved in 5  $\mu$ l ethanol). The opposite ear served as control (5  $\mu$ l ethanol). Ear thickness was determined (in 0.01-mm units) by using a dial thickness gauge (Mitutoyo, Japan) every 15 min for 90 min, starting immediately after archidonic acid application.

### Pain, central vs. peripheral

Pain perception on a hot plate is considered to be mediated by a central mechanism whereas the second, late phase of the response to an implantar injection of formalin reflects inflammatory pain mechanisms [Tjolson and Hole 1992].



Thus, central pain perception was assessed by the analgesic response on a hot plate (55°C, Columbus Instruments, OH, USA). Peripheral pain was measured by the response to implantar injection of formalin (4%) 45 min after injection of the drug.

#### *2.4 Statistical Analyses*

When 3 or more treatment groups were compared, data were analyzed with 1-way ANOVAs with Student Newman-Keul post-hoc tests. Two groups were analyzed with t-tests.

#### **Results**

(+)-CBD, which weakly binds CB<sub>1</sub> and CB<sub>2</sub> receptors, had no central neither peripheral (intestinal motility) effects (Fig. 1). Although all of the (+)-CBD analogues showed substantial CB<sub>1</sub> receptor binding (see Table I and Bisogno et al., 2001), only (+)-7-OH-CBD-DMH had central effects in all assays of the tetrad (Fig. 2 and Table I); (+)-CBD-DMH had a modest effect on rearing in an open-field (Fig. 2 and Table I). The experiment was repeated using (+)-CBD-DMH at least 5 times, and absence of central effects or small effects, was always found, usually in one or two assays (see Fig. 3 for a comparison with  $\Delta^9$ -THC).

However, all compounds, highly significantly inhibited defecation (almost always reducing fecal pellets to zero, see Fig 4 and Table I).

Centrally mediated pain in response to exposure to a hot plate (Fig 5) was not affected by (+)-CBD-DMH. In contrast, the second, inflammatory phase of the formalin-induced pain response [Tjolsen et al., 1992], was almost completely inhibited by (+)-CBD-DMH (Fig. 6).

Arachidonic acid-induced inflammation of the external ear was almost completely inhibited by 40 (Fig. 7A) or 10 (Fig. 7B) mg/kg of (+)-CBD-

DMH. (+)-CBD-DMH was as potent as indomethacin (Fig. 7A-B). (+)-7-OHCBDD-DMH (20mg/kg) also inhibited ear inflammation, but (+)-CBD had no effect (Fig. 7C).

*Receptor mechanism: effect of antagonists and CB<sub>1</sub><sup>-/-</sup> receptor knockout mice*

The inhibition of defecation induced by (+) CBD-DMH, was almost fully reversed by SR141716A (Fig 8), but not at all by 3 mg/kg SR1446528 (Fig 9).

A lower dose of SR144528 (1 mg/kg), also did not prevent intestinal immotility induced by (+)-CBD-DMH (data not shown).

None of the drugs assessed ((+)-CBD-DMH, (+)-7-OH-CBD-DMH and  $\Delta^9$ -THC had any effect in CB<sub>1</sub><sup>-/-</sup> receptor knockout mice, centrally (not shown) or peripherally on intestinal motility (Fig. 10).

Table 1

Compound	CBI/CB2 Receptor Binding (K <sub>i</sub> , $\mu$ M) <sup>5</sup>	Horizontal Move- ments (%MPE) <sup>1</sup>	Vertical Move- ments (%MPE) <sup>1</sup>	Catalepsy (Freezing of Move- ment) <sup>2</sup> (%MPE) <sup>2</sup>	Analgesia (Hot Plate) <sup>2</sup> (%MPE) <sup>2</sup>	Hypo- thermia ( $\Delta$ -Body Temp.) ( $^{\circ}$ C) <sup>3</sup>	Inhibition of Intestinal Motility (%MPE) <sup>4</sup>
$\Delta^9$ -THC	0.064/0.039	44*	12*	44*	45*	-2.1*	100*
+CBD	0.84/0.20 <sup>5</sup>	108	103	05	13	0.5	81
+CBD-DMH	0.017/0.211 <sup>5</sup>	82	61	16	10	-0.3	100*
+7OH-CBD	0.0053/0.101	107	81	0	77	0.3	89*
+7OH-CBD- DMH	0.0025/0.044 <sup>5</sup>	01*	0*	95*	100*	-5.2*	100*
+COOH- CBD	0.0132/0.322	80	71	06	100	-0.6	100*
+COOH- CBD-DMH	0.0058/0.156	102	100	0	100	0.2	100*

**Legend:** Central and peripheral effects of  $\Delta^9$ -THC, (+) CBD and two analogues.

Female Sabra mice (8-12 weeks old) were injected at a time interval, which had been shown previously to yield maximal effects (30 or 60 min) before testing in a series of 6 consecutive assessments: motor activity (ambulation and rearing) and defecation (intestinal motility) in an open field (for 8 min); catalepsy on an elevated ring (for 4 min); response to a painful stimulus (hot plate kept at 55  $^{\circ}$ C, mouse was allowed to remain on the plate for maximally 45 sec) and rectal temperature (hypothermia).

All groups consisted of 5 mice. All drugs were injected at 20 mg/kg in a mixture of Ethanol: Cremophor: Saline=1:1:18 ("Vehicle"). Each compound was tested at least twice, with almost identical results; several compounds (such as (+)CBD DMH and (+) 7OH CBD DMH were tested more than 5 times.

1) %MPE for Horizontal and Vertical movements was calculated as

$$\%MPE = 1 - \frac{Vehicle - Experimental}{Vehicle} \times 100\%$$

where MPE=maximal possible response, experimental=experimental animal's score  
2) %MPE for Freezing of Movements and for analgesia was calculated as

$$\%MPE = \frac{Experimental - Vehicle}{240 - Vehicle} \times 100\%$$

and

$$\%MPE = \frac{Experimental - Vehicle}{45 - Vehicle} \times 100\%$$

respectively.

3) Hypothermia was calculated as the difference between rectal temperature measured before in jection and 60 min. after injection.

4) Inhibition of Intestinal Motility was calculated as

$$\%MPE = \frac{Vehicle - Experimental}{Vehicle} \times 100\%$$

5) Data from Bisogno et al., 2001

6) Data from Shohami et al., 1996

\*) significantly different from vehicle controls (at least  $P < 0.05$ );  $nd$  = not determined

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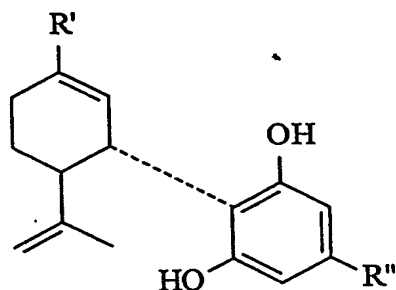
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## Claims:

1. An optically pure (+) enantiomer of a compound of the formula:



Formula I

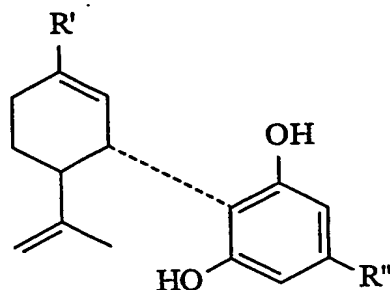
wherein R' designates a —COOH or —CH<sub>2</sub>OH group and R'' designates a straight or branched C<sub>5</sub>-C<sub>12</sub> alkyl group, an —OR''' group wherein R''' designates a straight or branched C<sub>5</sub>-C<sub>9</sub> alkyl group which may be optionally substituted with a phenyl group on the terminal carbon atom, or a —(CH<sub>2</sub>)<sub>n</sub>—O—C<sub>1-5</sub> alkyl group, wherein n is an integer of from 1 to 7, with the proviso that R' is not —CH<sub>2</sub>OH when R''' is dimethylheptyl, and pharmaceutically acceptable salts and esters thereof.

2. The (+) enantiomer of claim 1, wherein R' is —COOH and R''' is a pentyl or dimethylheptyl group.
3. The (+) enantiomer of claim 1, wherein R' is —CH<sub>2</sub>OH and R''' is a pentyl group.
4. A pharmaceutical composition containing as active ingredient a compound of formula I wherein the substituents are as defined in claim 1 and optionally further comprising at least one pharmaceutically acceptable carrier, additive, excipient or diluent.



5. The pharmaceutical composition of claim 4, optionally comprising an additional pharmaceutically active agent.

6. Use of a (+) enantiomer of a compound of the formula:



Formula Ia

wherein R' designates a CH<sub>3</sub>, —COOH or —CH<sub>2</sub>OH group and R'' designates a straight or branched C<sub>5</sub>-C<sub>12</sub> alkyl group, an —OR''' group wherein R''' designates a straight or branched C<sub>5</sub>-C<sub>9</sub> alkyl group which may be optionally substituted with a phenyl group on the terminal carbon atom, or a —(CH<sub>2</sub>)<sub>n</sub>—O—C<sub>1-5</sub> alkyl group, wherein n is an integer of from 1 to 7, or a pharmaceutically acceptable salt or ester as a selective modulator of the peripheral cannabinoid system.

8. Use of the (+) enantiomer of a compound of formula Ia as an analgesic agent.

9. Use of the (+) enantiomer of a compound of formula Ia as a modulator of the immune system.

10. Use of the (+) enantiomer of a compound of formula Ia as antiinflammatory agent.

11. Use of the (+) enantiomer of a compound of formula Ia as a modulator of the gastrointestinal tract.
12. Use of the (+) enantiomer of a compound of formula Ia as anti-diarrheal agent.
13. Use of a (+) enantiomer of a compound of the formula (Ia) wherein the substituents are as defined in claim 6 or a pharmaceutically acceptable salt or ester thereof, in the preparation of a pharmaceutical composition for the selective treatment of disorders associated with the peripheral cannabinoid system.
14. The use of claim 13, in the preparation of an analgesic pharmaceutical composition.
15. Use of the (+) enantiomer of a compound of formula Ia wherein the substituents are as defined in claim 6, in the preparation of a pharmaceutical composition for the treatment of immune disorders associated with the peripheral cannabinoid system.
16. The use of claim 15, in the preparation of an antiinflammatory agent.
17. Use of the (+) enantiomer of a compound of formula Ia wherein the substituents are as defined in claim 6 or a pharmaceutically acceptable salt or ester thereof, in the preparation of a pharmaceutical composition for the treatment of a disorder associated with the gastrointestinal tract.
18. The use of claim 17, in the preparation of an anti-diarrheal pharmaceutical composition.

19. A pharmaceutical composition for the selective treatment of disorders associated with the peripheral cannabinoid system comprising as active ingredient a compound of formula Ia.


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Figure 1

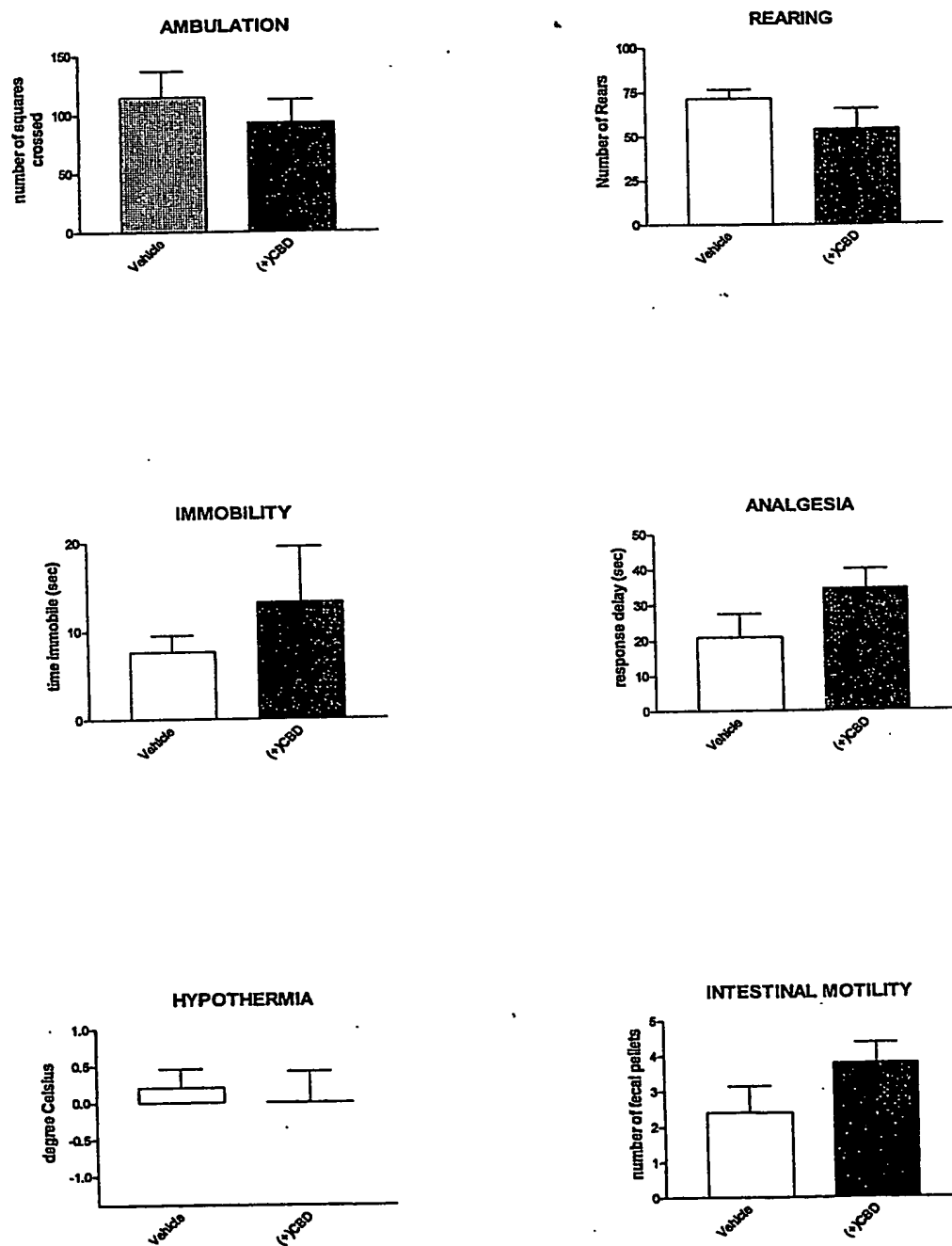


Figure 2

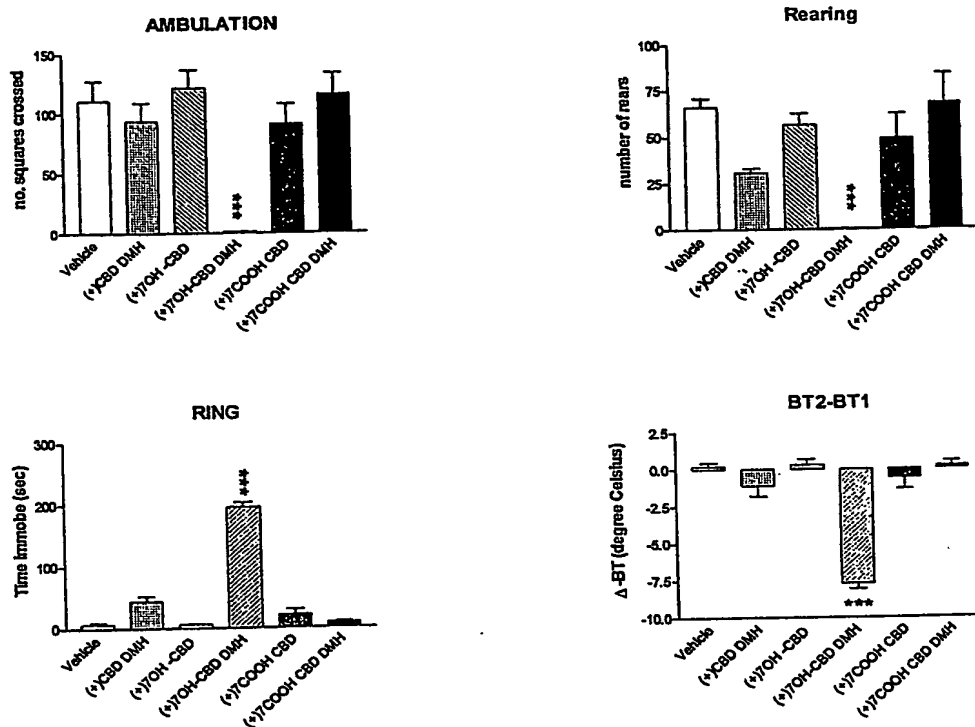


Figure 3

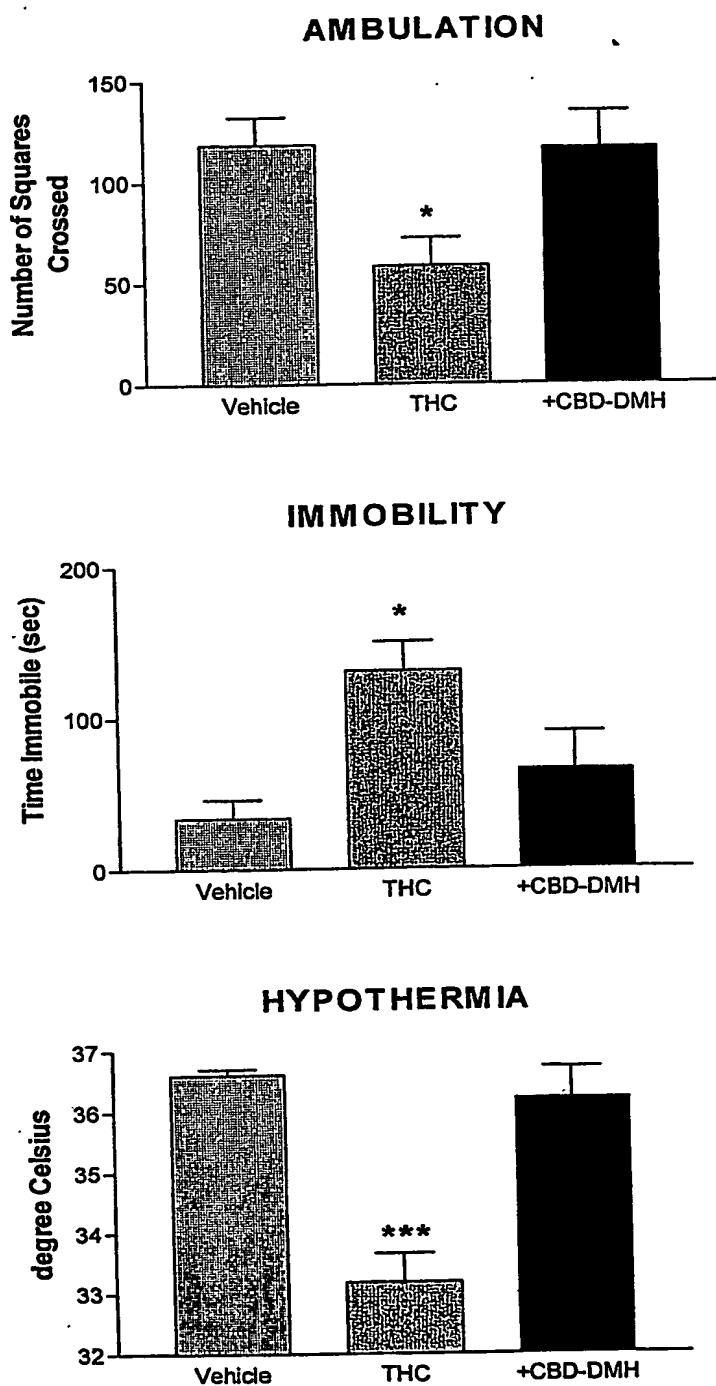


Figure 4

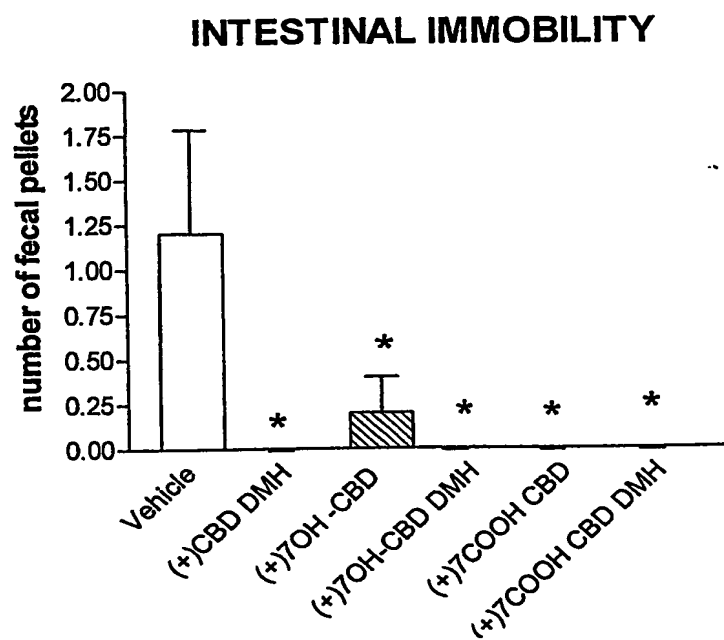
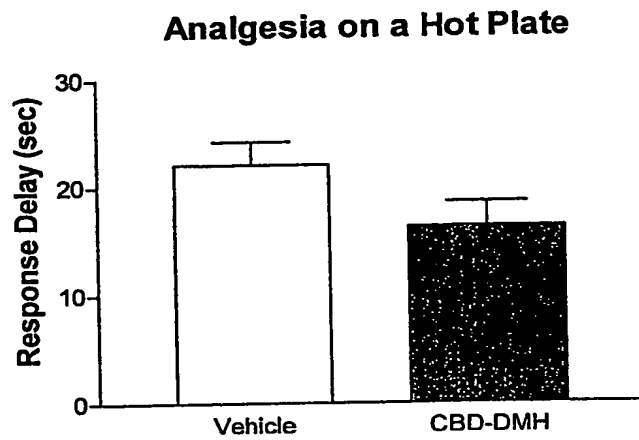
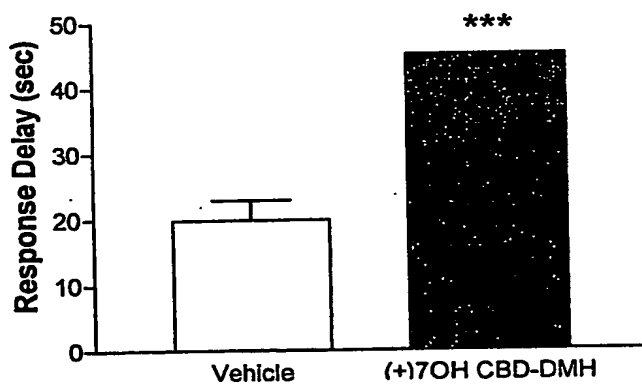


Figure 5



A

Figure 5



B



Figure 6

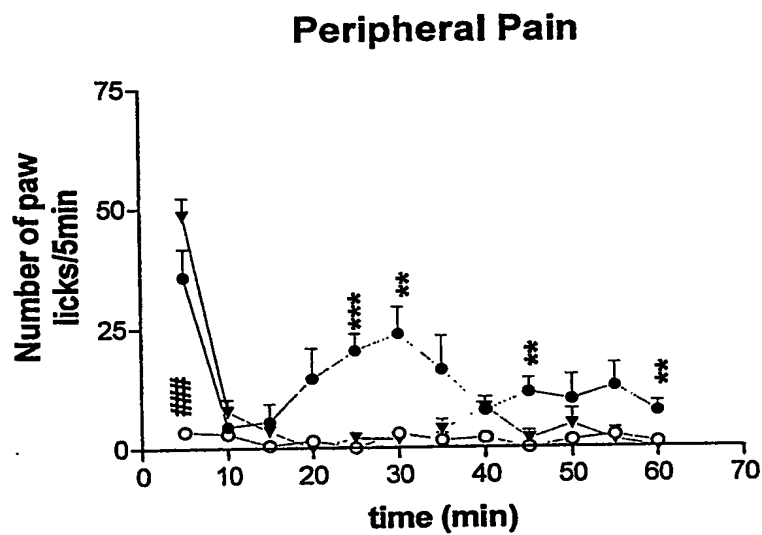


Figure 7A

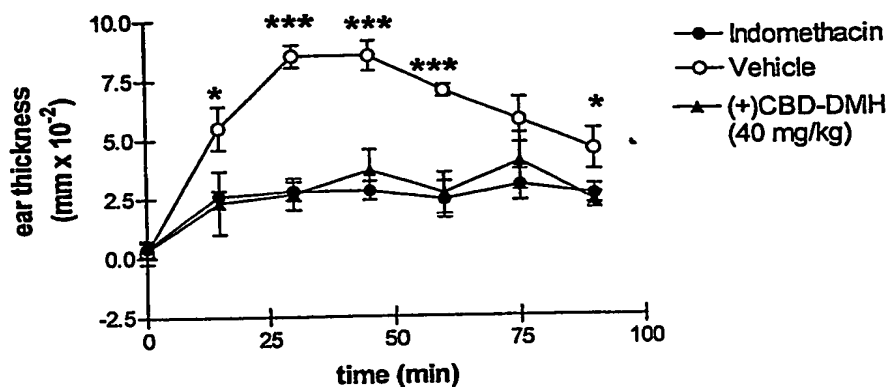


Figure 7B

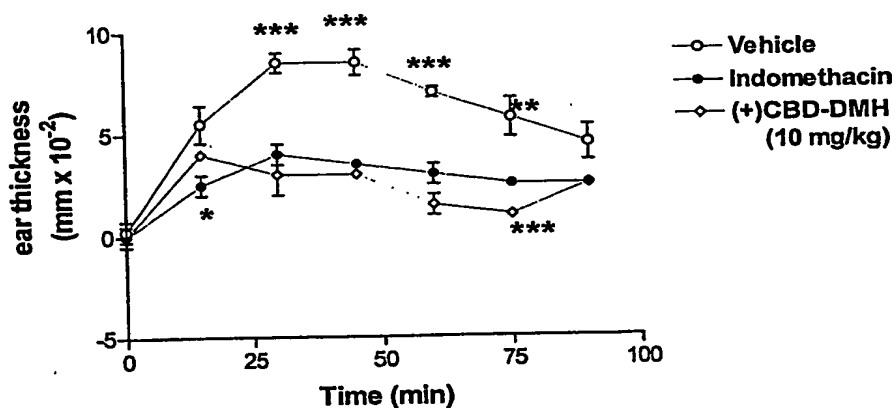


Figure 7C

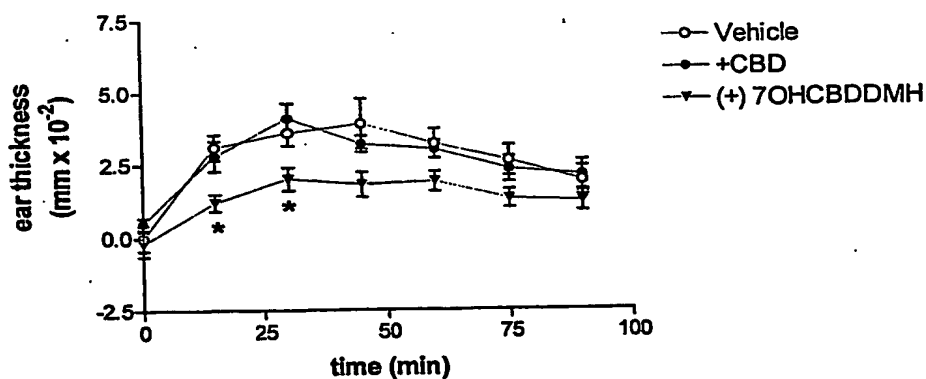


Figure 8

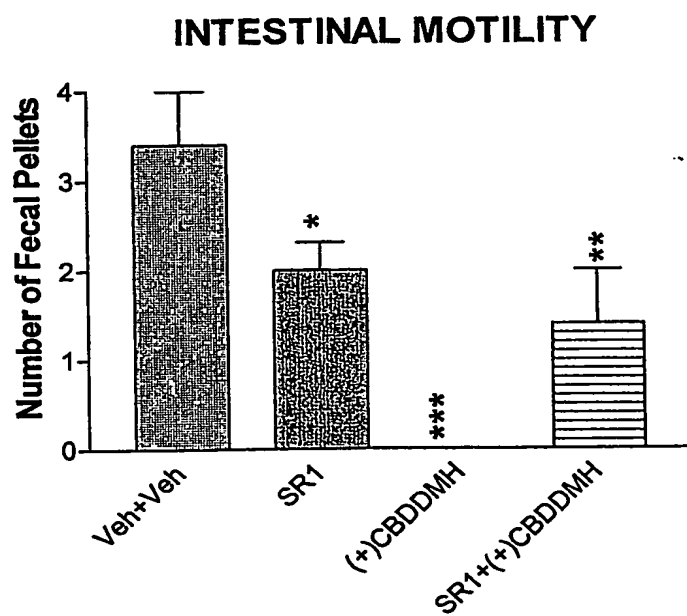


Figure 9

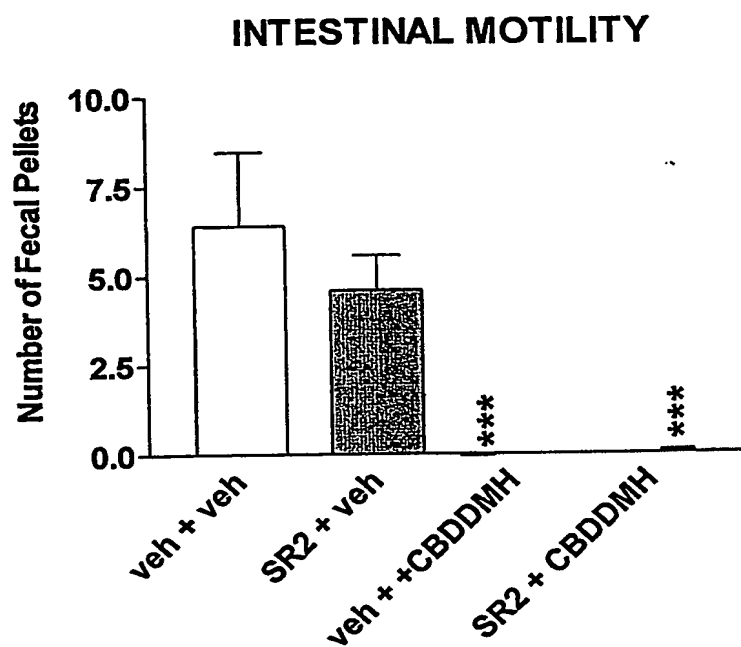
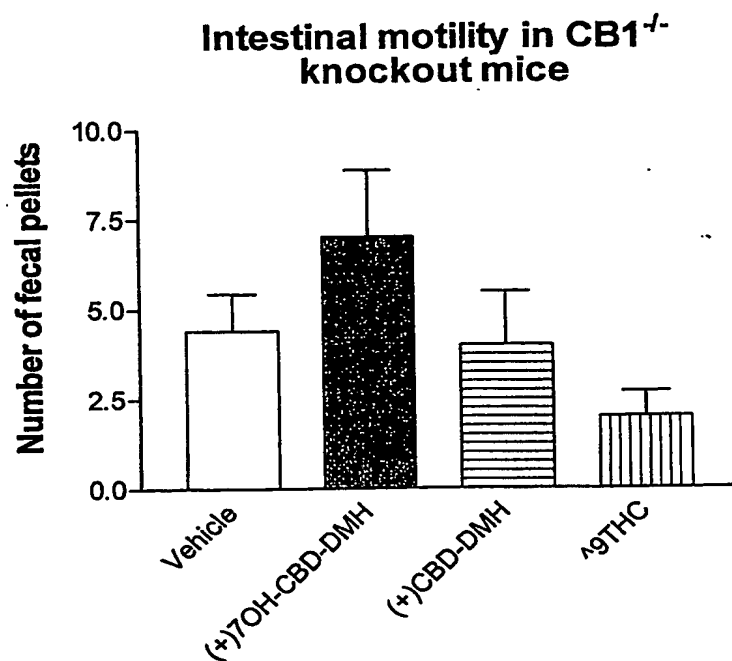


Figure 10



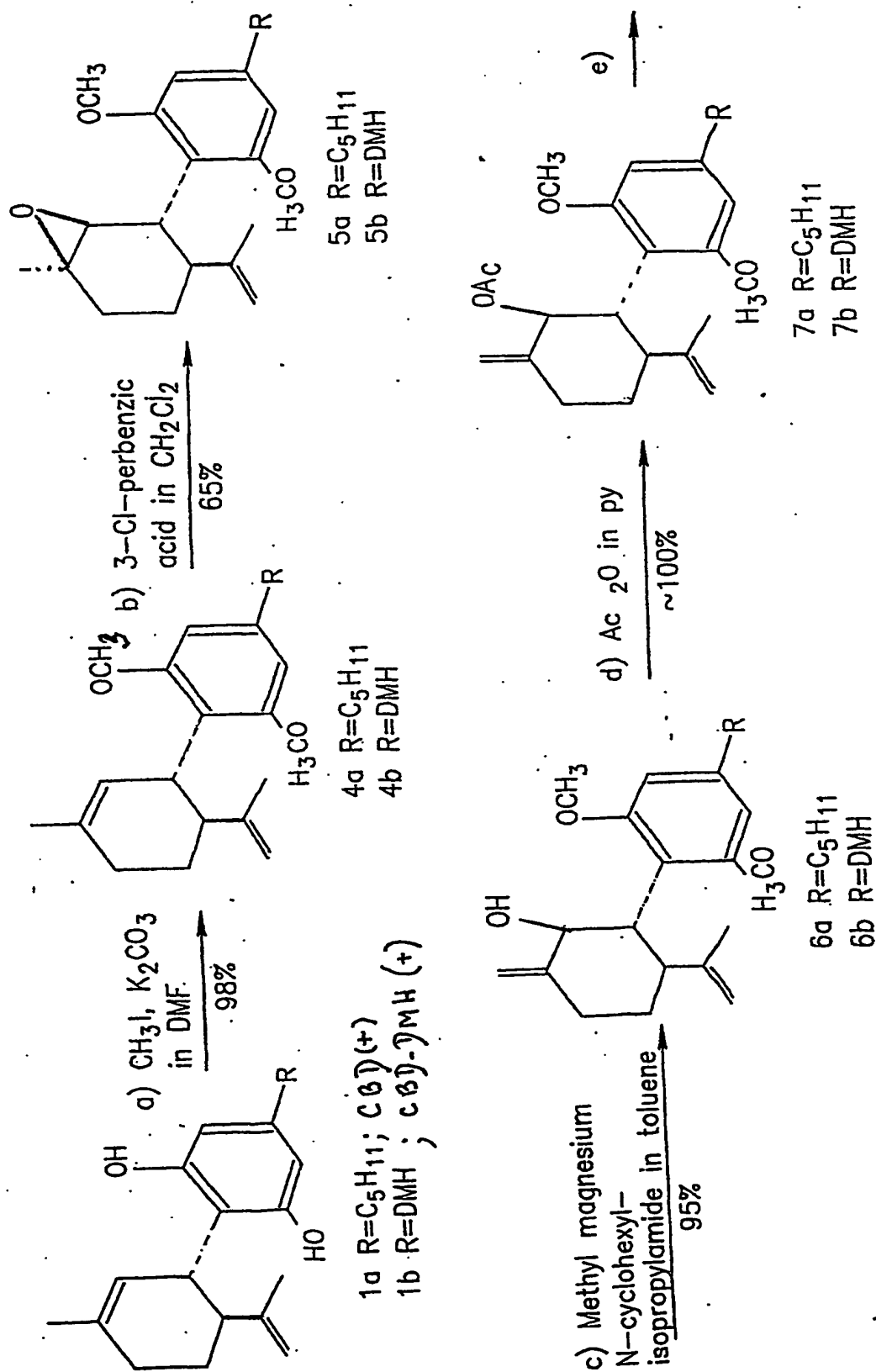


Fig. 11A

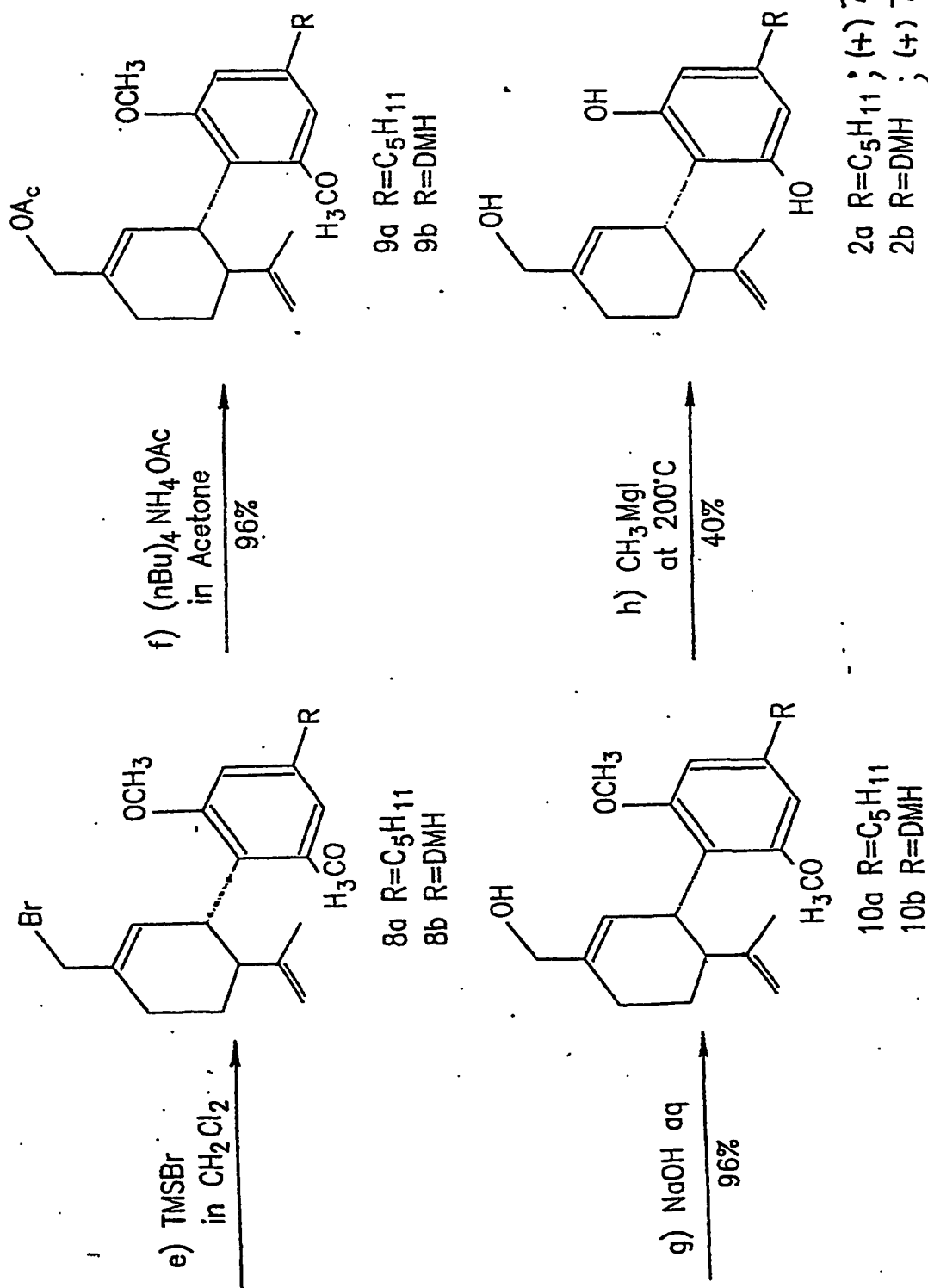


Fig. 11B

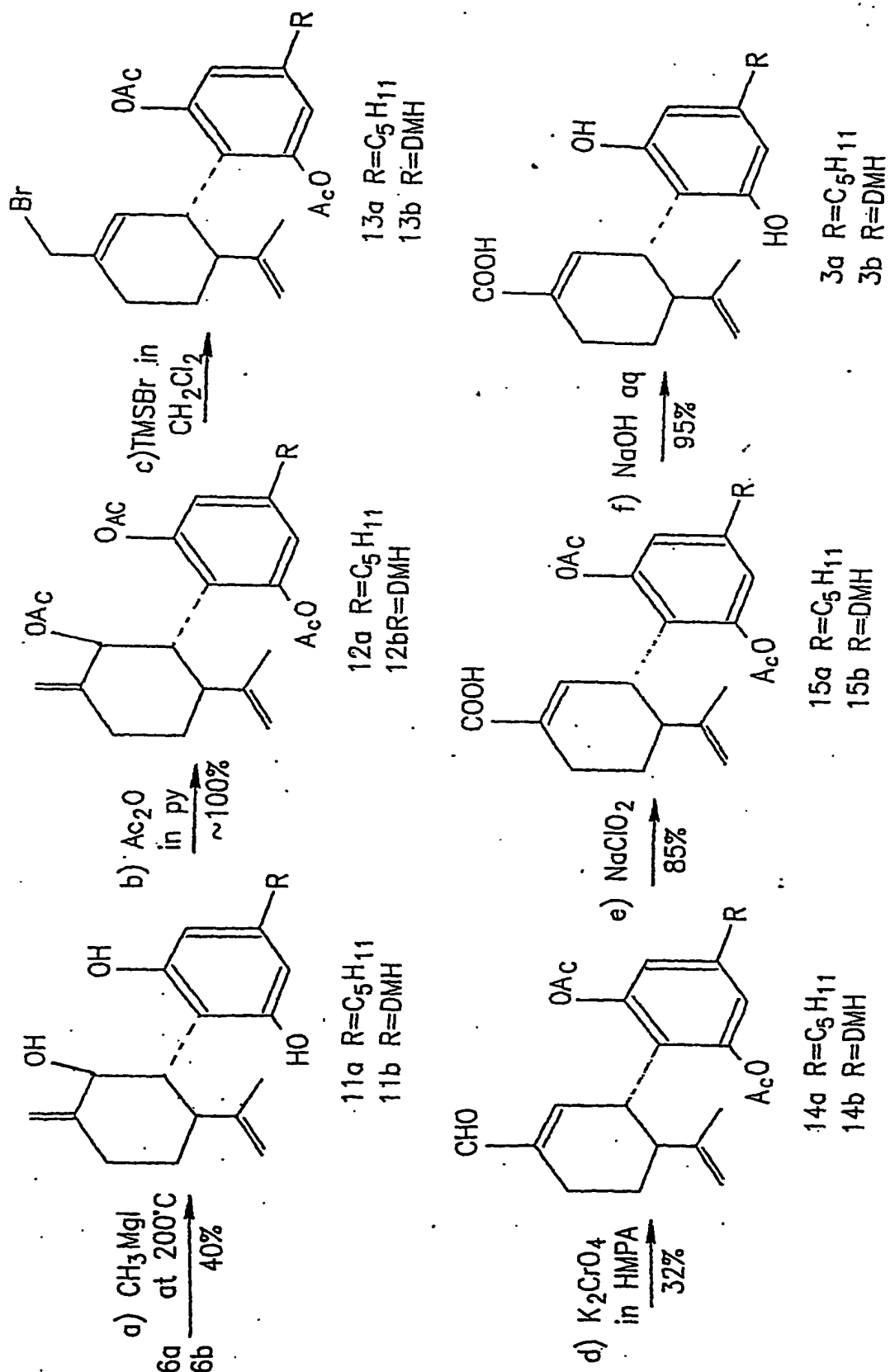


Fig.11C